Remarks

Claims 1-43, 72-75 and 83-91 are pending. Claims 44-71, 76-82 and 92-132 have been withdrawn from consideration. Claims 133-141 have been added as new claims and support for these claims can be found at least in the original claims.

I. Election Restriction

Applicants note the election of Group I (claims 1-43. 72-75, and 83-91) but maintain the traversal of the restriction.

II. Information Disclosure Statement

The Examiner notes that the Information Disclosure Statement filed June 24, 2004 failed to comply with 37 CFR § 1.98(a)(2), as the Information Disclosure Statement did not provide a legible copy of each U.S. and foreign patent and each publication. The Applicant acknowledges and apologizes for this oversight and submits the required copies herewith, along with the fee of $180.00 under 37 C.F.R. § 1.17(p) for filing Information Disclosure Statement under 37 C.F.R. § 1.97(c). Applicant respectfully requests and appreciates consideration of the publications cited therein.

III. Rejection under 35 U.S.C. § 101

Claims 1-4, and 72 were rejected herein under 35 U.S.C. § 101 for allegedly being directed to non-statutory subject matter. The Office Action argues that claims 1-6 read on human HEX-α and HEX-β genes. The Examiner has indicated that amending the claim to include "isolated" would alleviate this issue, but this is unnecessary as the composition of claim 1 is directed to a "single" nucleic acid, "wherein the nucleic acid comprises a sequence encoding a HEX-α and a sequence encoding a HEX-β". Thus, claims 1-4 and 72 require that HEX-α and HEX-β to be on a single nucleic acid. In a human, HEX-α and HEX-β are located on

chromosomes 15 (see XM_037778) and 5 (see XM_032554), respectfully, and in mouse on chromosome 9 (see NM_010421) and 13 (see NM_010422), respectfully. Thus, there is no single nucleic acid in humans (or mice) comprising sequences encoding both HEX-α and HEX-β. Claims 1-4 and 72 are therefore directed to statutory subject matter, and the applicant respectfully requests the withdrawal of this rejection and allowance of claims 1-4 and 72.

IV. Rejection under 35 U.S.C. § 112, first paragraph

Claims 1-13, 15-18, 20-22, 24-31, 39-43, 72-75, 84-88, 90 are rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the written description requirement. The Examiner argues that the claim(s) contain subject matter not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The Examiner states that no guidance is given in the claims as to what HexA, HexB, a constitutive promoter, and a cell specific promoter are. The Examiner further states that claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which are not conventional in the art as of the Application's effective filing date.

Through review of the Examiner's argument, Applicants understand that the Examiner believes 1) the use of the name of a gene, such as HexA and HexB, is insufficient to clearly define what is encompassed by these names and that the skilled artisan cannot envision all of the family members denoted by these names (Office Action at p. 5, l. 12, and p. 6, ll. 4-6), 2), the skilled artisan cannot envision all sequences that would qualify as a constitutive promoter and cell specific promoter because the skilled artisan cannot predict where these promoters will express and what effect they will have, (Office Action at p.6 ll. 8-10, and p. 6, ll. 13-16) and 3) claims 12 and 16 are too broad because a skilled artisan cannot envision all possible single amino acid combinations which can be substituted while preserving activity nor can the skilled artisan envision all possible combinations up to 70% identity to SEQ ID NOs 3 and 1 (Office Action p.

7, ll. 11-15). Applicant addresses each of these individually below, after a general discussion of the law surrounding written description.

A. Written Description Law

While there are many aspects and nuances to the courts' interpretation of the written description requirement under 35 U.S.C. § 112, first paragraph, only those aspects directly addressing the legal position of the Office Action are addressed. The Office Action correctly states that one can adequately meet the requirements of the written description requirement by "describing the invention with sufficient relevant identifying characteristics (as it relates to the invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention (citing Pfaff v. Wells Electronics, Inc. 48 USPQ2d 1641, 1646 (1998), *emphasis in original*). However, contrary to the position of the Office Action, this standard does *not* require that the skilled artisan be able to "envision all members of a genus" (Office Action at p. 6, ll. 4-6) nor that the skilled artisan be able to "reasonably predict" a particular level of activity, (Office Action, p. 6, ll. 12-16) nor that "conception is not achieved until reduction to practice has occurred" (Office Action, p. 7, l. 16) nor that "adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of identifying it." (Office Action, p. 7, ll. 16-20). No case that the Examiner has relied upon supports these positions, and furthermore, there is none that the Applicant is aware.

It has been repeated over and over by the Federal Circuit that "the written description requirement can be met by "show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ... i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." Enzo Biochem vs. Gen-Probe Incorporated, 296 F.3d 1316, 1324, 63 U.S.P.Q.2d 1609 citing the Written Description Guidelines, 66 Fed. Reg. at 1106. As noted by the Examiner, this standard,

as well as many others is viewed through the eyes of the skilled artisan. As discussed below, there can be no doubt that claims 1-13, 15-18, 20-22, 24-31, 39-43, 72-75, 84-88, 90 meet this standard.

Regents of the University of California v. Eli Lilly and Company, 119 F.3d 1559, 1567, 43 U.S.P.Q.2d 1398 (Fed. Cir. 1997) held that a method of obtaining an unknown gene was not adequate written description for the gene itself when nothing was known about the structure of the gene itself. As will be discussed below, this is factually very different than the compositions of claims 1-13, 15-18, 20-22, 24-31, 39-43, 72-75, 84-88, 90, where structure is known and provided in the specification.

A patent application preferably omits that which is well-known or common knowledge to those of ordinary skill in the art.[1] Thus, an applicant should not be penalized for leaving out information in his patent application that those of ordinary skill in the art knew or could readily have obtained at the time of the filing of the patent application.

B. A gene name is allegedly insufficient to define what is encompassed in a claim

Applicants are aware of no case holding that a gene name is insufficient to describe a nucleic acid or protein if that gene name connotes to the skilled artisan possession of the composition, such as by structure or identifying characteristics. The structures of Hex-α and Hex-β are well known, as well as homologues of these, and the skilled artisan is capable, based on the information in the application as well as on that which is known about Hex-α and Hex-β and biotechnology, to determine if a particular protein is a Hex-α and Hex-β protein.

[1] "[A] . . . specification need not disclose what is well known in the art." (*Lindemann Maschinenfabrik v. Am. Hoist and Derrick,* 730 F.2d 1452, 1463 (Fed. Cir. 1984) (citing *In re Myers*, 410 F.2d 420 (CCPA 1969). See also *Hybritech Inc. v. Monoclonal Antibodies, Inc.*802 F.2d 1367, 1384 (Fed. Cir. 1986).

For example, direction as to what Hex-α and Hex-β can be found in the specification. The specification makes it clear that a Hex-α and Hex-β are two polypeptides that produce β-hexosaminidase which is a lysosomal acidic hydrolase. For example the specification states,

> β-hexosaminidase is a hetero or homo dimer made up of two subunits arising from two separate genes, HexA and HexB (p. 1, ll. 17-19)

Furthermore, the specification states,

> The catabolism of the GM_2 ganglioside in mammalian cells is mediated by β-hexosaminidase, a lysosomal acidic hydrolase. The lysosomal enzyme β-hexosaminidase (HEX) is comprised of 2 subunits (peptides), HEX-α and HEX-β, encoded by two distinct genes, HexA and HexB, respectively. β-hexosaminidase exists in 3 isoforms (proteins), HEXA (α/β heterodimer), HEXB (β/β homodimer) and HEXS (α/α homodimer) (p. 14, ll. 27-32).

Thus, it is clear that a Hex-α and Hex-β are polypeptides that care capable of forming a functional β-hexosaminidase. In addition the application is replete with examples of models related to deficiencies of β-hexosaminidase and ways of testing and identifying deficiencies of β-hexosaminidase. Thus the skilled artisan is taught by the specification how to know or understand when a functional β-hexosaminidase is present. There is little doubt that the skilled artisan would understand what was meant with the terms Hex-α and Hex-β, and that the inventor was in possession of the molecules, particularly in light of the mandate by Maschinenfabrik v. Am. Hoist and Derrick that an application preferably omits that which is already known by the skilled artisan.

C. The skilled artisan allegedly cannot envision all sequences that would qualify as a constitutive promoter and cell specific promoter

The Examiner argues that the skilled artisan cannot envision all sequences that would qualify as a constitutive promoter (claim 17) or a cell specific promoter (claim 87). The examiner

bases this argument on the position that one skilled in the art cannot reasonably envision all sequences that qualify for these promoters or predict where these promoters will express and what effects expression of a transgene will have on these cells. The Applicant respectfully disagrees.

As discussed herein, and agreed to by the Examiner, the standard for written description is whether the skilled artisan would understand that the Inventor was in possession of the claimed invention at the time of filing the application. The specification provides extensive discussion about promoters, both constitutive and regulated. (See for example, p. 53, l. 1 to p. 56, l. 6 where not only constitutive and regulated promoters are discussed generally but multiple specific examples and sequences of different types of each are provided, in for example, SEQ ID NOs: 21-41). The specification provides more than enough information about promoters for the skilled artisan to use any type of promoter that may be desired.

Furthermore, the skill in the art, with respect to promoters is extensive. Certainly since the isolation of the CMV promoter and its use in expression of a heterologous construct system, back at least as of January. 30, 1985, (United States Patent No. 5,385,839 for "Transfer vectors and microorganisms containing human cytomegalovirus immediate-early promoter regulatory DNA sequence" and 5,168,062 for "Transfer vectors and microorganisms containing human cytomegalovirus immediate-early promoter-regulatory DNA sequence") the skill of the identification and use of both constitutive and regulatable promoters has only grown. The use of constitutive and cell specific promoters is well established in the art and the selection of these promoters requires only routine experimentation to evaluate the expression and effects of the selected promoter and transgene.

The issues of expression and where expression occurs, respectfully, are not relevant to the question of whether there is written description for the use of the word "promoter." This is solely determined by whether the skilled artisan would understand that the inventor was in possession of the use of a promoter, any promoter, within the vectors and nucleic acids claimed.

There can be little doubt that sufficient guidance exists in the application to both make and use any nucleic acid having any promoter as claimed in claims 1-13, 15-18, 20-22, 24-31, 39-43, 72-75, 84-88, 90.

In light of the edict that an application preferably omit that which is known by the skilled artisan (Maschinenfabrik v. Am. Hoist and Derrick), Applicants have surely provided enough information about both constitutive and regulatable promoters to meet the written description requirement.

D. The skilled artisan allegedly cannot envision all members of claims 12 and 16

The Examiner argues that the specification does not teach how to make HEX-α or HEX-β with 70-99% sequence similarity to that of SEQ ID NOs:3 and 1, nor does it teach how to predict what amino acid substitutions and combinations up to 70% sequence identity of SEQ ID NOs:3 and 1 would result in viable HEX-α or HEX-β.

The USPTO has already established that variants can be claimed based on sequence identity (see Example 14 of the U.S.P.T.O. "Synopsis of Application of Written Description Guidelines"), wherein it is stated:

> "[t]he single species disclosed is representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of an assay which applicant provided for identifying all of the at least 95% identical variants...which are capable of the specified catalytic activity." (page 54, fourth paragraph)

For the sake of argument, in a complex sequence, the issue of *envisioning all members* with 95% identity, which the Examiner is concerned with, would also be present, as it is allegedly present for compositions having 70% identity. The PTO has understood, however, in the issuance of the Guidelines, that "envisioning" all members is not the standard for written description nor is it required. (Applicants note that if required, however, every sequence having 70% identity to SEQ ID NO:1 or 3 could be written out, merely by the recitation of SEQ ID

NO:1 and 3. Although there would be many many sequences and it might take someone many years to actually sit and write each on a piece of paper, a high school biology student with the genetic code table in one hand and a systematic method of making each substitution in the other, could write each sequence. This point will not be argued further, however, as the standard does not require this).

The issue then becomes, if the principle of defining a genus of genetically related compositions by their identity is a viable way of describing a genus because the genus all has a common structural identity, then the only thing left is the extent of the functional identity that should be allowed in claims 12 and 16.

In this regard, it is generally understood that a molecule with 70% or greater homology to a known sequence will have the essential physical properties of the identified structure. For example, it has been demonstrated using pairwise sequence comparison that enzyme function is well conserved when a sequence identity is above 40%, and more importantly that 60% identity is sufficient for at least 90% retention of functional conservation, and that enzyme function does not *start* to diverge, *at all*, until the sequence identity is below 70% (see Tian, W. and Skolnick, J. J Mol Biol. 2003 Oct 31;333(4):863-82, attached herewith). Thus, contrary to the Examiner's position that the Applicant won't know which sequences function and which do not, at 70% identity, the Applicant would expect with a very high level of certainty that any given sequence would function, and this is assuming that no information about amino acids that are important for function is known (which is not the facts in the present application, as discussed extensively through out the present application certain mutations are well known to cause neurodegenerative diseases). If one factors in this knowledge to the analysis, the skilled artisan would likely never pick a sequence that would not function.

Further, while the skilled artisan has a high expectation that any given sequence having 70% identity would function, if needed, it is routine experimentation for one skilled in the art to test such variants to determine if they fit into the claimed homology and to assay said variant for

functionality. Provided there is some type of assay in the specification, such as a model system to assay the disclosed compositions. The specification states:

> "A model system for the study of these vectors is a mouse that is knockout mouse deficient in both HexA and HexB, since the *hexA*$^{-/-}$/*hexB*$^{-/-}$ mouse is characterized by global disruption of the *hexA* and *hexB* genes. Gene disruption in this mouse is global, and therefore, can be used as a model for global replacement." (Page 41, lines 18-21).

Thus, the concerns of the Examiner, that not all members can be envisioned and that there is no way to determine which members have functional activity, can be removed.

Contrary to position of the Office Action with respect to Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993), Amgen Inc. v Chugai Pharaceuticals Co. Ltd., 18 USPQ2d 1016 (Fed. Cir. 1991) and Fiddes v. Baird, 30 USPQ2d 1481, 1483, reduction to practice of each member of a genus is not required. Furthermore, Fiers, Amgen, and Fiddes, all support the state of the law as set forth in Lilly and Enzo, for example, that some structure with a means to identify the function of members of the genus is sufficient to describe a genus of compounds that are both structurally and functionally related, such as the structures set forth in claims 1-13, 15-18, 20-22, 24-31, 39-43, 72-75, 84-88, 90. Furthermore, as discussed above, in the present application, these cases can also be distinguished in that the structure of the composition being claimed is provided in the specification, and in Fiers and Lilly, the structure of the composition being claimed was unknown. Applicants also respectfully point out that the reference to "conception" in the context of the present rejection is misplaced as the rejection is not dealing with a 35 U.S.C. 102(g) rejection as was the case in certain subparts of both Fiers and Amgen.

The Applicant respectfully requests the withdrawal of the rejection, and allowance of claims 1-13, 15-18, 20-22, 24-31, 39-43, 72-75, 84-88, 90.

V. Rejection under 35 U.S.C. § 112, second paragraph

Claims 12, 13, 15, 16, 73, 74, 75 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The specification provides extensive guidance as to what identity means at, for example, p. 58, l. 3 to p. 59 to l. 23. It is clear from the context of the claim and the description in the specification that identity is referring to the complete molecule. Thus, for example, in the situation set forth in the Office Action at p. 10, where the Examiner is discussing a truncation of a protein with a subsequent comparison, it is clear from the specification and the claims that a protein lacking 30% of the sequence of SEQ ID NO:1 or SEQ ID NO:3 in claims 12 and 16 would have only a 70% identity to SEQ ID NO:1 or SEQ ID NO:3 because it is being compared to "the sequence set forth in SEQ ID NO:1" or "the sequence set forth in SEQ ID NO:3." The claims are clear and unambiguous as originally written.

With respect to the Examiner's concern with the claims covering fusion proteins, it is undeniable that the specification enables the making of fusion proteins and that these types of proteins are well known by the skilled artisan. In fact, the very technology extensively described in the Examples and Specification utilizes technology that is exactly the same as the technology utilized to make fusion proteins. The claims are not unclear and ambiguous because they read on fusion proteins. Furthermore, while this rejection was made under 35 U.S.C. § 112, second paragraph, the language used by the Examiner is "make and use" language, which is only appropriate under a 35 U.S.C. § 112, first paragraph rejection. In any event, the claims are fully enabled as the technology of fusion proteins was well understood at the time of the filing of the present priority application.

The Examiner further argues that the word "conservative" is a relative term. The specification provides ample discussion of what "conservative" means, at least at pages 66, line 2

to 67, line 5, including Table 2, and exemplified on page 68, line 22. Given the present specification, one skilled in the art would clearly understand whether a change to a nucleic acid or amino acid sequence was a conservative change.

The Examiner further argues that the word "stringent," as used in the specification to define conditions of hybridization, is a relative term. In response, the Application provides explicit guidance to the skilled artisan as to what "stringent" means and how it can be determined at, for example, page 60, ll. 3-29. Stringent hybridization conditions are empirically and routinely determined based on the target sequence. The application provides extensive guidance as to how to perform this.

The applicant contends that one of skill in the art would understand what is meant by percent identity, conservative substitution, and stringent hybridization based on the state of the art and what is taught in the specification and therefore respectfully requests the withdrawal of the rejection.

VI. Rejection under 35 U.S.C. § 102

Claims 1-4 were rejected under 35 U.S.C. § 102 as allegedly being anticipated by Nakai et al. (1991, Cytogenet. Cell Genet. 56:164), Wood et al. (1989, Nucleic Acid Research, 17:2368), and Belsham and Sonenberg (1996, Microbiological Reviews, 60:499-511). As discussed above, there is no single nucleic acid in humans comprising sequences encoding both HEX-α and HEX-β. Claims 1-4 therefore do not read on humans, and the applicant respectfully requests the withdrawal of this rejection.

VII. Rejection under 35 U.S.C. § 103(a)

Claims 1-41, 72-75, 83-91 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Poeschla et al.(1998, Nature Medicine, 4: 354-357) and Jang et al. (1989,

Journal of Virology, 63:1651-1660) in view of the NCBI Annotation Project, Beccari, et al., Triggs-Raine et al., Yonemura et al., Armentano et al., Sloan and Virgin, Henninghausen and Fleckenstein, Suminaga et al., and Muyazaki et al. The Examiner notes that Poeschla et al. demonstrated that a FIV vector can infect human cells and drive reporter gene expression.

It is undeniable that in making a determination of obviousness under 35 U.S.C. § 103, the Examiner must establish a *prima facie* case that (1) the prior art suggests the invention developed, and (2) the prior art indicates that the invention would have a reasonable likelihood of success. In re Dow Chem. Co., 837 F.2d 469, 5 U.S.P.Q.2d 1529 (Fed. Cir. 1988); In re Geiger, 815 F.2d 686, 2 U.S.P.Q.2d 1276 (Fed. Cir. 1987). In order for a reference to be effective prior art under 35 U.S.C. § 103, it must provide a motivation whereby one of ordinary skill in the art would be led to do that which the appellant has done. Stratoflex, Inc. v. Aeroquip Corp., 713 F.2d 1530, 1535, 218 USPQ 871, 876 (Fed. Cir. 1983).

A situation where it would be obvious to try or test is a particular construct or method is insufficient to meet the standard of obviousness. The current rejections are analogous to the rejection deemed improper by the Federal Circuit (In re Deuel, 34 USPQ2d 1210 (Fed. Cir. 1995)). In Deuel, the Court reaffirmed that a rejection based on an "obvious to try" standard was improper. The Court specifically found that prior art that teaches a method for obtaining a general result, when the actual results are unknown, is insufficient to make obvious the actual results obtained upon which the claims are based. In pertinent part, the Deuel Court states

> "A general motivation to search for some gene that exists does not necessarily make obvious a specifically-defined gene that is subsequently obtained as a result of that search."
>
> > "Thus, even if, as the examiner stated, the existence of general cloning techniques, coupled with knowledge of a protein's structure, might have provided motivation to prepare a cDNA or made it obvious to prepare a cDNA, that does not necessarily make obvious a particular claimed cDNA. 'Obvious to try' has long been held not to constitute obviousness". Id.

Furthermore, it is axiomatic that evidence which teaches away from the claimed compositions or molecules provides significant evidence of non-obviousness.

A. Claims 1-41, 72-75, 83-91 are not obvious

1. No suggestion or motivation present or provided

a) Mere presentation of sequence is insufficient to make a combination of sequences obvious

The Office Action cites Beccari, et al., Triggs-Raine et al., Yonemura et al., Armentano et al., Sloan and Virgin, Henninghausen and Fleckenstein, Suminaga et al., and Muyazaki et al. as allegedly providing one or more pieces of the complete nucleic acids present in one or more of claims 1-41, 72-75, 83-91. First, there is no suggestion or motivation provided by these references, or other references, to arrive at the claimed nucleic acids. This suggestion or motivation is necessary. Alone or in combination, these references fail to even make a *prima facie* case of obviousness. For the sake of brevity, Applicants are not currently arguing whether the references actually teach the specific sequences recited in the specification as their combination fails, even if the sequences are correct. However, Applicants reserve the right to argue this, should it be found that a prima facie case of obviousness is established by the mere referral to references containing alleged subparts of a claimed nucleic acid.

b) No motivation suggestion to combine in Poeschla et al. or Jang et al.

Neither Jang et al. nor Poeschla et al. provide a motivation to combine HEX-α and HEX-β into a single vector with an IRES sequence such that these vectors can be expressed in the brain.

At least, Jang et al. (1989) do not teach the following which would at least be necessary to make claims 1-41, 72-75, 83-91 obvious and there is not motivation or suggestion to combine any other reference to alleviate these deficiencies. Jang et al. (1989) does not teach the expression of both HEX-α and HEX-β from a bicistronic gene. This, at least, would be required to make claims 1-41, 72-75, 83-91 obvious. Moreover, Jang et al. does not teach the construction of lentiviral bicistronic vectors. In addition, Jang et al. does not teach the expression of any set of two genes by an IRES-barring bicistronic vector in whole animals in vivo. Jang et al do not teach about the order of the bicistronic gene comprised of HEX-β and HEX-α.

At least, Poeschla et al. do not teach the following which would at least be necessary to make claims 1-41, 72-75, 83-91 obvious and there is not a motivation or suggestion to combine any other reference to alleviate these deficiencies. Poeschla et al. does not teach anything about HEX-α and HEX-β. Poeschla et al. does not teach anything about IRES sequences. Poeschla et al. does not teach anything about the use of the lentiviral vector to transduce brain cells. Poeschla et al. does not teach anything about the treatment or amelioration of Tay Sachs or Sandoff's diseases, for example. Poeschla et al. does not teach anything about the order of the bicistronic gene comprised of HEX-β and HEX-α.

Applicants understand the Office Action's combination rejection to be summarized as follows: 1) the individual pieces of the claimed nucleic acids were known (p. 13 of the Office Action), 2) Poeschla et al. showed that FIV vectors could infect cells (p. 14, ll. 1-12 of the Office Action), and 3) Jang et al. allegedly teach the expression of two proteins from a bicistronic gene using an IRES sequence (all of which may be an over-interpretation) (p. 14, l. 13 to p. 15, l. 10) with the conclusion being,

> "One having ordinary still in the art would have been motivated to these genes [referring to the HEXA and HEXB genes I believe] one for the other, in order to obtain a FIV or a HIV system which

> can be used to infect cells and to express one's gene(s) of choice." (p. 16, ll. 3-5 of the Office Action).

The Examiner has attempted to combine 10 references to arrive at the present rejection, and has not pointed to a single spot in any of the references where there was a even a hint, much less a suggestion or motivation, to arrive at the claimed nucleic acids. The mere assertion that the skilled artisan would have been motivated is insufficient to meet a case for *prima facie* obviousness. No argument, much less evidence, that the skilled artisan would be so motivated is provided. More is needed when only two references are combined. Surely when a combination of 10 references is used, there must also be more, and there needs to be, at least a suggestion to combine any two of the 10 references, and even this is lacking in the present rejection.

2. Reasonable Expectation of Success

A reasonable expectation of success is required for a *prima facie* case of obviousness. The Examiner has provided no evidence that a reasonable expectation of success that the claimed compositions, all of which are based on HEX-β and HEX-α, being expressed such that they would produce β-hexosamindase, would work. The Examiner has merely asserted,

> There would have been a reasonable expectation of success given the results of Poeschla et al. and Jang et al. demonstrating the ability to transfect replicating and non-replicating human cells, to be able to express genes from these vectors, and to be able to express more than one gene from these vectors to deliver multiple gene products to cells. (p. 16, ll. 6-10 of the Office Action).

There is no mention of the success of HEX-β and HEX-α in combination and there is no mention that this combination would have a reasonable expectation of success that these two proteins would come together to form a functional β-hexosaminidase enzyme. Thus, there is no *prima facie* case made for obviousness.

3. Secondary considerations

It is clear, that even if a *prima facie* case of obviousness is made, which Applicants dispute here, the *prima facie* case of obviousness can be rebutted by what have been called secondary factors. One of the secondary factors that makes something non-obvious is a teaching away from the claimed invention. In this case, there is just such a teaching. Previous attempts to provide HEX-β and HEX-α in vivo, *on separate plasmids, much less a single plasmid*, were unsuccessful. Thus, the starting point for the skilled artisan was that nucleic acids and vectors sufficient for gene therapy related to HEX-β and HEX-α did *not* work. How can the skilled artisan have had a reasonable expectation that the claimed nucleic acids would work in this environment?

A simple substitution of the reporter gene lacZ by HEX-α or HEX-β would not have been efficacious in restoring the activity of a functional β-hexosaminidase enzyme (α/β hetero-dimmer) as taught by the work of Guidotti et al. (Guidotti JE, Mignon A, Haase G, et al. Adenoviral gene therapy of the Tay-Sachs disease in hexosaminidase A-deficient knock-out mice. Hum Mol Gen 8, 831-838, 1999). Specifically, Guidotti et al. demonstrated that administration of viral vectors (adenoviral gene therapy) encoding for HEX-α or HEX-β alone **were not** sufficient in restoring β-hexosaminidase activity *in vivo*. Furthermore, simultaneous administration of such adenoviral vectors resulted in a very high HexA activity in the liver (9-fold more than the normal value) and in partial or total correction in other tissues: 95% of the normal activity in the heart, 51% in skeletal muscle, 40% in spleen and 34% in kidney. Furthermore, Guidotti et al. did not see activity in the brain. Guidotti et al. shows that, "the activity in the brain was not significantly increased". (p. 832, col 2, ll. 18-19). In contrast the *in vivo* date provided in the present specification shows that the claimed bicistronic vectors do provide significant expression in the brain.

Not only must the HEX-α and HEX-β subunits be expressed, the HEX-α and HEX-β subunits must properly and stoichiometrically associate and come to the formation of a single

functional β-hexosaminidase enzyme (α/β hetero-dimmer): HEX-α peptide must associate with one HEX-β peptide. However, two HEX-α peptides can associate to form the protein HEX-S, as well as two HEX-β peptides can associate to form the protein HEX-B. However, only the association of one HEX-A and one HEX-B peptide results in the formation of a functional β-hexosaminidase enzyme capable of metabolizing the GM2 ganglioside, storage of which results in the development of Tay-Sachs or Sandhoff disease. Moreover, the HEX-β peptide has higher affinity for it self than HEX-α for it self, resulting in a competition between the HEX-α and HEX-β subunits in the formation of the various isoforms of β-hexosaminidase (HEX-A, HEX-B and HEX-S). Subsequently, HEX-β must exist in over-abundance in the micro-environment for HEX-β to associate with HEX-α in the formation of a functional β-hexosaminidase enzyme (α/β hetero-dimmer).

There is nothing that would lead one to the claimed nucleic acids to have this type of result, and there is nothing that would provide a reasonable expectation of success that the claimed nucleic acids would function. In fact, it is just the opposite, as taught by Guidotti et al., one did not even think they could be *expressed* appropriately in the brain. Applicant therefore respectfully requests the withdrawal of this rejection

A Credit Card Payment Form PTO-2038 authorizing payment in the amount of $180.00, for the filing of an Information Disclosure Statement after receiving a first Office Action, is enclosed. Also included with this amendment is an Information Disclosure Statement, a corresponding PTO-1449, and the references cited therein, as well as a copy of Tian, W. and Skolnick, J. J Mol Biol. 2003 Oct 31;333(4):863-82, the court cases, and patents cited herein. This amount is believed to be correct; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

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I hereby certify that this correspondence, including any items indicated as attached or included, is being deposited with the United States Postal Service as express mail label No. **EL 970612066 US** in an envelope addressed to: Mail Stop AMENDMENT, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date indicated below.

Scott Darnell — 3-7-05

Scott Darnell — Date